Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 1, 9, 12, and 115 have been amended. Claims 180–184 have been added. Support for the new claims may be found in the specification at page 14, lines 10–14 (claim 184); page 39, line 16 through page 40, line 9 (claim 180); Tables 1 (claims 181 and 182), 2 (claim 183), 3 (claim 182), and 4 (claim 182); and Figures 2 and 3 (claim 184). Claims 109–179 have been withdrawn. Claims 1–16, and 109–184 are pending.

The withdrawal from consideration of claims 109–121 and 138–144 is respectfully traversed. Applicant hereby requests reconsideration of the withdrawal of claims 109–121 and 138–144, which are directed to compositions and kits, respectively, that include a fusion polypeptide according to claim 16. Claims 109–121 and 138–144 are related to claim 16 as combination-subcombination. *See* MPEP § 806.05(c). Restriction between a combination and a subcombination is proper only if the U.S. Patent and Trademark Office ("PTO") can demonstrate that the combination as claimed (a) does not require the particulars of the subcombination as claimed for patentability (to show novelty and unobviousness), and (b) the subcombination can be shown to have utility either by itself or in another materially different combination. MPEP § 806.05(c). The PTO has not (and cannot) demonstrate that both these requirements are satisfied. In particular, because combination claims 109–121 and 138–144 depend from and, as claimed, require the particulars of subcombination claim 16, applicant submits that the PTO cannot satisfy the first requirement. Hence, restriction is not proper between these claims, and should be withdrawn.

Although method of use claims 122–137 and 145–179 stand withdrawn, these method claims should be rejoined upon allowance of the product claims upon which they depend. M.P.E.P. § 806.05(h); *In re Ochiai*, 71 F.3d 1565, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1995). Because claims 1 and 16 are allowable for the reasons noted below, applicant respectfully requests rejoinder of claims 122–137 upon allowance of claims 1 and 16, and rejoinder of claims 145–179 upon allowance of claim 1.

The rejection of claims 1–16 under 35 U.S.C. § 112 (first para.) for lack of enablement is respectfully traversed.

Claim 1 relates to a fibronectin type III polypeptide monobody. The polypeptide monobody includes at least two Fn3 β-strand domain sequences with a loop

region sequence linked between adjacent β-strand domain sequences; and optionally, an N-terminal tail of at least about 2 amino acids, a C-terminal tail of at least about 2 amino acids, or both. At least one loop region sequence, the N-terminal tail, or the C-terminal tail includes an amino acid sequence which varies by deletion, insertion, or replacement of at least two amino acids from a corresponding loop region, N-terminal tail, or C-terminal tail in a tenth Fn3 domain of fibronectin, and the polypeptide monobody exhibits nuclear receptor binding activity.

The PTO's position is that the specification is enabling for monobodies constructed from SEQ ID NO: 2, but not for monobodies constructed from any other wild-type fibronectin. Applicant respectfully disagrees, because a high degree of conservation exists among mammalian tenth Fn3 domains and the basis asserted by the PTO is irrelevant to the claimed monobodies. *See* Declaration of Shohei Koide under 37 CFR § 1.132 ("Koide Decl.") ¶ 4.

Mammalian tenth Fn3 domains of fibronectin are highly conserved. Alignment of mouse, chimp, dog, cattle, and rat tenth Fn3 domains with SEQ ID NO: 2 (human) showed that these sequences are between 86–100% conserved relative to the human Fn3 sequence of SEQ ID NO: 2. Koide Decl. ¶ 5. The β-strand sequences are highly conserved (β-strands A, F, and G) or identical (β-strands B, C, D, and E). *Id.* The loop regions are mildly conserved (loop E-F), highly conserved (loops B-C and C-D), or identical (loops A-B, D-E, and F-G).

Based on the structural homology, a person of skill in the art of molecular biology, protein biochemistry and/or protein engineering would fully expect mammalian tenth Fn3 domains that are highly similar to the human Fn3 domain of SEQ ID NO: 2 to be useful as a starting scaffold for preparing functional polypeptide monobodies that bind to a nuclear receptor of interest. Koide Decl. ¶ 6.

The PTO has cited Garcia-Pardo et al., "Primary Structure of Human Plasma Fibronectin," *J. Biol. Chem.* 260(18):10320–10325 (1985) ("Garcia-Pardo") as evidence that mammalian fibronectin is structurally diverse. The teachings of Garcia-Pardo are irrelevant to the claimed invention because the region of fibronectin that was analyzed by Garcia-Pardo is distinct of the tenth Fn3 domain that is used as a starting scaffold for preparing the claimed monobodies. Koide Decl. ¶ 8. Indeed, Garcia-Pardo implies that its 31-kDa fragment is not even an Fn3 domain, let alone the tenth Fn3 domain. *Id.*

The PTO has also cited to evidence of mutational instability of proteins other than the tenth Fn3 domain of fibronectin, citing to Mickle & Cutting, "Genotype–Phenotype Relationships in Cystic Fibrosis," *Med. Clin. North Am.* 84(3):597–607 (2000) for the example of cystic fibrosis transmembrane conductance regulator, DONALD VOET & JUDITH G. VOET, BIOCHEMISTRY 126–128, 230 (1990) ("Voet") for the example of the hemoglobin beta subunit, and Yan et al., "Two–Amino Acid Molecular Switch in an Epithelial Morphogen that Regulates Binding to Two Distinct Receptors," *Science* 290(5491):523–527 (2000) for the example of ectodysplasin. The PTO has failed to demonstrate how these unrelated proteins are relevant to the tenth Fn3 domain of fibronectin. The recitation of isolated incidents of drastic mutational effects does not demonstrate that most (or even many) mutations have effects of such magnitude. Koide Decl. ¶ 9. Indeed, Voet states that mutations can change a protein "in ways that do not significantly affect its function," and teaches that critical residues and non-critical residues can be identified by comparing homologous proteins. DONALD VOET & JUDITH G. VOET, BIOCHEMISTRY 186 (3d ed. 2004); Koide Decl. ¶ 9. Moreover, for the reasons discussed below, mutational effects are not unpredictable.

In the context of the present invention, mutational effects are not unpredictable for several reasons. First, the claimed invention relates to mutations of loop regions spanning between adjacent β-strands or to the N-terminal or C-terminal sequences. Koide Decl. ¶ 10. That is, the structural integrity of the β-strands present in the starting scaffold are maintained in the polypeptide monobodies. *Id.* This allows the person of skill to expect the resulting mutant polypeptides to be structurally similar, while their binding activity to nuclear receptors may vary. *Id.* The structure/function relationship is described at page 13, lines 26–27 (β-strands) and page 14, lines 5–9 (loop region sequence, N-terminal tail, and C-terminal tail) of the present application. Second, even if the resulting mutant polypeptides were structurally unsound (i.e., inherently unable to bind a nuclear receptor), the present application teaches how to perform a library selection to obtain only monobodies that exhibit nuclear receptor binding affinity. *See* Examples 1 and 2; Koide Decl. ¶ 10. In other words, if a fraction of monobodies in the library were non-functional, those non-functional monobodies would be screened out. Koide Decl. ¶ 10. Therefore, one of skill in the art would know from the specification how to make and identify monobodies according to the claimed invention. *Id.*

For these reasons, one of skill in the art reading the present specification would know how to construct monobodies that have nuclear receptor binding affinity from fibronectin tenth Fn3 domains other than the scaffold of SEQ ID NO: 2. Therefore, the lack of enablement rejection is improper and should be withdrawn.

The rejection of claims 1–16 under 35 U.S.C. § 112 (first para.) for lack of written description is respectfully traversed in view of the above amendments. For substantially the same reasons as noted above, one of ordinary skill in the art would fully recognize that applicants were in possession of polypeptide monobodies constructed from other fibronectin tenth Fn3 domains.

The burden of establishing that an application lacks adequate written descriptive support falls on the PTO. *See In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."). According to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (January 5, 2001) ("Written Description Guidelines"), when the genus represents widely variant species more than one species is required, yet when the genus represents closely related species as few as one species may be sufficient. 66 Fed. Reg. at 1106. Thus, size of the genus is clearly of less import than variance of species within the genus.

In this case, applicant has identified a wild-type (SEQ ID NO: 2) sequence and over 50 mutant (SEQ ID NO: 3 and the mutations set forth in Tables 2–4) sequences derived therefrom. In addition, applicant has demonstrated that mammalian tenth Fn3 domains are not highly variant. See Koide Decl. ¶ 5.

Because of the high degree of identity and conservation among mammalian tenth Fn3 domains, particularly among β-strands thereof, it is appropriate to consider the human Fn3 domain of SEQ ID NO: 2 as representative of mammalian tenth Fn3 domains generally. The PTO, on the other hand, has provided no evidence concerning variance within the genus. Instead, the PTO cites to Garcia-Pardo to support its position that the genus is highly variable, yet, as discussed above, Garcia-Pardo is not relevant to the claimed invention. Knowing that one or more species may adequately define a genus lacking substantial variation, one of skill in the art would understand that applicants were in possession of the presently recited genus. Because the PTO has failed to meet its burden of

establishing that the present claims lack written descriptive support, the rejection of claims 1–16 for lack of written description is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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